IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Moore et al.

Application Number: 09/263,626

Group Art Unit: 1646

Filed: March 5, 1999

Examiner: Brannock, M.

Title: Cytokine Receptor Common Gamma Chain Like

Attny. Docket No.: **PF466**

#20
B.Q.J
2/14/02

DECLARATION OF THI-SAU MIGONE UNDER 37 C. F. R. § 1.132

I, Thi-Sau Migone, do hereby declare and state:

1. I am a citizen of Italy, residing at 308 Midsummer Drive, Gaithersburg, MD 20878.

2. Since November 1st, 1999, I am currently employed as Senior Scientist I of Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, Maryland 20850, (HGS), assignee of the captioned application. In 1991, I received my Ph.D. in Biological Sciences from the Department of Biochemistry at the University of Pavia, Italy. From 1992 to 1996, I served as a post-doctoral fellow at the National Institutes of Health, Bethesda MD in the Laboratory of Molecular Immunology, where I studied regulation of cytokine signaling in T cells. From 1997 to 1999, I served as a post-doctoral fellow at the DNAX Institute Cellular and Molecular Biology, Palo Alto CA in the Department of Cell Signaling, where I continued to study the regulation of cytokine signaling in T cells. I joined HGS in 1999 in the position of Scientist. I have authored over 20 articles that have been published in peer-reviewed scientific journals. A copy of my curriculum vitae is attached hereto as Exhibit A. TSM

3. I have been shown and have examined U.S. Patent Application No. 09/263,626, (the 626 Application) captioned above, which I understand was filed on March 5, 1999.

4. I have been asked by patent counsel for HGS to provide my understanding of: (a) the

extent to which the 626 Application directs an immunologist to the understanding that the Cytokine Receptor Common Gamma Chain Like (CRCGCL) receptor protein of the invention is involved in the proliferation of T cells; and (b) that soluble CRCGCL polypeptides can be used antagonistically to reduce the proliferative activity of the CRCGCL receptor.

5. In particular, I have read and noted the following portions of the 626 Application. Isolated polynucleotides encoding a CRCGCL receptor protein having the amino acid sequence are shown in Figure 1A-B (SEQ ID NO:2). Figure 2 of the 626 Application shows an alignment of CRCGCL and the translation product of closest homology, the Bos Taurus Interleukin-2 receptor common gamma chain (shown as Accession No. gi/1532088 aa), which illustrates the sequence homology between the two.

6. I note that the 626 Application discusses the various conserved domains revealed in the amino acid sequence alignment with the Interleukin–2 receptor gamma chain, shown in Figure 2, and that based upon this homology, the application states that the CRCGCL receptor protein may be involved in the differentiation and proliferation of cells, as follows:

> Using BLAST analysis, SEQ ID NO:2 was found to be homologous to members of the Cytokine Receptor family. Particularly, SEQ ID NO:2 contains domains homologous to the translation product of the Bos Taurus mRNA for Interleukin-2 receptor gamma (Accession Nos. 1532088) (Figure 2) (SEQ ID NO:3), including the following conserved domains: (a) a predicted transmembrane domain located at about amino acids 226-260; (b) a predicted WXWS (SEQ ID NO:5), or [STGL]-x-W-[SG]-x-W-S (SEQ ID NO:18), domain located at about amino acids 198-204 (T-x-P-S-x-W-S) (SEQ ID NO:19), although not a perfect match; and (c) a predicted Jak Box, having the motif W(P,E)X(V,I)P(N,S,D)P (SEQ ID NO:20), domain located at about amino acids 261-268 (I-P-X-V-P-D-P) (SEQ ID NO:21), although not a perfect match. These polypeptide fragments of CRCGCL are specifically contemplated in the present invention. Because Interleukin-2 receptor gamma (Accession Nos. 1532088) is thought to be important as a cytokine receptor, the homology between Interleukin-2 receptor gamma (Accession Nos. 1532088) and CRCGCL suggests that CRCGCL may also be involved in the differentiation and proliferation of cells. CRCGCL is also homologous to other Interleukin-2 receptor gamma genes isolated from a variety of species, such as human (Accession No. gi/349632), Canis familiaris (Accession No. gi/517412), and mouse (pri/S37582).

See page 7, line 24 to page 8, line 4.

7. It was known in the field of cytokine research that the interleukin-2 (IL-2) receptor common gamma chain (gamma c), is important for the growth and differentiation of immune cells, such as T and B lymphocytes, natural killer cells, macrophages, and monocytes. *See* Discussion, page 336, of Lin et al., Immunity, Vol. 2:331-339 (1995), attached herewith as Exhibit B. Furthermore, it was also known that the cytokines IL-2, IL-4, IL-7, IL-9 and IL-15 are known T cell growth factors that all use the common gamma chain receptor. *See* Introduction, page 331, second column of Lin et al. These facts are clearly stated in the application at page 1, lines 25-28.

8. I also note that the 626 Application states that CRCGCL receptor protein interacts with a member of the Janus kinase ("Jak") and therefore indicates that the CRCGCL receptor protein is involved in proliferation and differentiation, as follows:

> Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.
>
> There is preliminary data that CRCGCL interacts with Jak1.
>
> *See* page 85, line 32 to page 86, line 1.

9. The observation of the CRCGCL receptor protein's interaction with a Janus kinase is consistent with what was known in the field of cytokine research, namely that cytokine receptors primarily use the Jak-STAT signaling pathway and therefore play an important role in controlling the immune response. *See* O'Shea, J., Immunity, Vol. 7:1-11 (1997), submitted herein as Exhibit C. This knowledge is also reflected in the application at page 86, Table 1 which lists many growth factors and cytokines known to activate the Jak-STAT pathway.

10. Further, in 1995, receptor reconstitution studies showed the necessity of co-expressing IL-2 receptor gamma chain with the IL-7 receptor to be able to stimulate gene activation and hence, mediate proliferative signals. *See* Abstract, Ziegler et al., Eur. J. Immunol., Vol. 25(2):399-404 (1995), submitted herein as Exhibit D.

11. In addition, I note that the 626 Application explicitly describes the tissue distribution of the CRCGCL receptor protein, as follows:

> Clone HTAEK53 was isolated from an activated T-cell cDNA library.
>
> *See* page 7, line 2.
>
> Subsequent Northern analysis also showed a 1.6 Kb transcript in a cervical cancer cell line (HeLa), activated T cells, and a lung carcinoma cell line (A549), while a shorter variant is also expressed in the lymph node and to a lesser extent in the spleen tissues, a pattern consistent with immune specific expression.
>
> *See* page 7, lines 15-18.

12. Further, I note that the 626 Application explicitly states where CRCGCL receptor protein is not expressed, as follows:

> CRCGCL expression was not observed in the following cell lines, HL60, K562, Molt-4, Raji, SW480, G361, as well as the heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, thymus, prostate, testis, ovary, small intestine, colon, or peripheral blood leukocytes, a pattern consistent with immune specific expression.
>
> *See* page 7, lines 19-23.

13. From paragraphs 11 and 12, I understand that CRCGCL receptor protein is an immune specific receptor that is not only expressed in T-cells, but more specifically, its expression is limited to activated T-cells as opposed to resting T-cells. This is expressly stated in the 626 Application on page 8, line 32 which states that "[d]istribution is only activated T-cells..."

14. As a result, the 626 Application concludes that based upon its tissue distribution in activated T cells and homology to an IL-2 receptor, the CRCGCL receptor protein can be used to diagnose or treat immune and autoimmune disorders, as follows:

> Because CRCGCL was isolated from activated T cells, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders. Distribution in only activated T-cells and homology to the cytokine receptors IL2 and IL13 suggests that this protein is a novel member of the cytokine receptor family expressed specifically on T-cells.
>
> *See* page 8, lines 21-23.

The tissue distribution of this gene in cells of the immune system suggests that the protein product of this clone would be useful for treatment, prophylaxis and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, AIDS. In addition, its expression in T-cells suggests a potential role in the treatment, prophylaxis and detection of thymus disorders such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism and hypothyroidism. The receptor could also serve as a target for small molecule or monoclonal antibody, blocking its activity, which could be important in the disease states listed herein.

See page 8, line 34 to page 9, line 6.

CRCGCL polypeptides or polynucleotides may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells.

See page 56, lines 2-12.

CRCGCL polynucleotides or polypeptides may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of CRCGCL polypeptides or polynucleotides that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

See page 57, lines 1-8.

15. Furthermore, the 626 Application suggests that soluble CRCGCL receptor can be useful as an antagonist to diagnose or treat immune-related diseases, as follows:

Moreover, CRCGCL polypeptides can be used to treat disease. For example, patients can be administered CRCGCL polypeptides in an effort to replace absent or decreased levels of the CRCGCL polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

See page 45, lines 19-27.

16. The conclusions stated in paragraphs 14 and 15 are consistent with what is known in the field of cytokine research. Specifically, mutations of the common gamma chain results in X-linked severe combined immunodeficiency (XSCID) in humans. *See* Lin et al. at 331,

first column. Further, studies in common gamma chain knock-out mice show phenotypically abnormal T-cells (*see* O'Shea at page 2, second column).

17. As discussed above in paragraphs 5-16, the 626 Application instructs that the CRCGCL receptor protein is (1) homologous to an IL-2 receptor common gamma chain; (2) expressed only in activated T cells; (3) possesses a Jak box; and (4) interacts with a Jak kinase. An immunologist, after reading these statements made in the 626 Application and based upon what was known in the field of cytokine research, would understand that the 626 Application is directed to the use of the CRCGCL receptor protein as a positive regulator of T cell proliferation and would also understand that the CRCGCL receptor protein antagonist is useful for inhibiting T cell proliferation and therefore will be useful to treat certain immune disorders, particularly those related to T cells.

18. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereupon.

2.7.02
Date

Thi-Sau Migone
Thi-Sau Migone, Ph.D.